

# Advanced Cutaneous Squamous Cell Carcinoma of the Trunk and Extremity: Analysis of Prognostic Factors

JAMES H. NORTH JR., MD, FACS,\* JAMES E. SPELLMAN, MD, FACS, DEBORAH DRISCOLL, BA, AUGUSTINE VELEZ, MD, FACS, WILLIAM G. KRAYBILL, MD, FACS, AND NICHOLAS J. PETRELLI MD, FACS

*Soft Tissue, Melanoma and Bone Service, Division of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, New York*

**Background:** Patients with squamous cell carcinoma (SCC) of the skin may exhibit locally advanced or metastatic disease and present a challenging management problem.

**Methods:** A retrospective review of 40 patients with advanced SCC of the trunk or extremity managed at Roswell Park Cancer Institute from 1982 through 1992 was performed to identify clinical and pathologic factors that influenced outcome.

**Results:** There were 27 males and 13 females with a median age of 61 years. Median follow-up was 24 months. Surgical resection to control the primary tumor was often extensive. Amputation was required in nine patients, hemipelvectomy in three patients, and hemicorporectomy in one patient. Median survival was 28 months, and 5-year survival was 43%. Univariate analysis identified stage ( $P = 0.04$ ), size ( $P = 0.0001$ ), type of surgical procedure ( $P = 0.009$ ), and margins of resection ( $P = 0.005$ ) as having prognostic significance. On multivariate analysis, stage ( $P = 0.04$ ) and size ( $P = 0.02$ ) were found to be significant.

**Conclusions:** Optimum treatment for advanced SCC of the trunk and extremity involves surgical resection with uninvolved margins. The role of elective node dissection remains undefined. Investigation is needed to define the role of neoadjuvant therapy that may improve functional and cosmetic results. *J. Surg. Oncol.* 64:212-217, 1997 © 1997 Wiley-Liss, Inc.

**KEY WORDS:** epidermoid carcinoma; extremity; lymph nodes; Marjolin's ulcer; skin; squamous cell carcinoma; paraneoplastic syndrome

## INTRODUCTION

An estimated 140,000 new cases of squamous cell carcinoma (SCC) of the skin occur each year in the United States [1]. These tumors usually present as a localized lesion that is amenable to surgical excision for cure. Due to delayed recognition, a subset of patients may present with locally advanced disease or with regional lymphatic metastases. The management of these patients can prove challenging and may involve radical resection or lymph node dissection, often coupled with a multimodality approach. Information concerning the management and prognosis of patients with advanced cutaneous squamous cell carcinoma is scarce.

In the present series, we investigate clinical and pathologic factors that affect the outcome of patients managed with advanced cutaneous squamous cell carcinoma of the trunk and extremities.

## MATERIALS AND METHODS

Forty patients managed at Roswell Park Cancer Institute (RPCI) during the period January 1, 1982 to Decem-

\*Correspondence to: James H. North Jr., M.D., General Surgery Service, Eisenhower Army Medical Center, Fort Gordon, GA 30905. Fax 706-787-2347

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**TABLE I. Incidence of Signs and Symptoms in 40 Patients With Advanced Cutaneous Squamous Cell Carcinoma of the Trunk and Extremity at Time of Presentation**

Sign/Symptom	No. patients (%)
Increase in size	32 (80)
Ulceration	20 (50)
Pain	17 (40)
Bleeding	2 (5)

ber 3, 1992, with locally advanced or metastatic squamous cell carcinoma arising from an extremity or truncal primary, were reviewed. Small superficial cancers managed by simple excision and tumors arising on the skin of the head and neck were excluded. Squamous cell tumors of the anus or genitalia were also excluded.

Clinical characteristics at presentation, therapeutic interventions, and patient outcomes were analyzed. Patients were staged according to the 1993 recommendations of the American Joint Committee on Cancer (AJCC) [2]. Pathology was reviewed by the Department of Pathology at RPCI. Factors assessed for prognostic significance were sex, location of tumor, tumor size, depth, grade and stage, presence and number of lymph node metastases, type of surgical resection, and margins of surgical resection. Survival distributions were calculated by the method of Kaplan and Meier [3]. Tests of significance with respect to survival distributions were based on the log-rank test [4]. Cox's proportional hazards model was used for the multivariate analysis [4]. Significance was defined as  $P < 0.05$ .

## RESULTS

Forty patients were treated at RPCI for advanced SCC of the skin of the trunk or extremity from 1982 through 1992. There were 27 males (68%) and 13 females (32%). The median age was 61.0 years (range 28–87 years). There were 27 patients (68%) who were referred to RPCI after receiving some form of therapy elsewhere. Nine patients (22%) were referred after biopsy only. Only four patients (10%) presented to our institution de novo.

Signs and symptoms were noted in 39 patients (Table I). Most patients presented with a lesion that was increasing in size or was ulcerating. Chronic inflammation was associated with the development of SCC in 16 of the 40 patients (40%). This included five patients (12%) who were paraplegic and had SCC arise in chronic decubitus ulcers. SCC was associated with a long-standing pilonidal cyst in three patients (8%), whereas an additional three patients had SCC arise at the site of a long-standing wart (upper extremity digit in one patient and plantar warts in two patients). A history of trauma to the site and a prolonged history of a nonhealing wound was noted in two patients (5%). Additionally, two patients (5%) had

**TABLE II. Anatomic Location of Squamous Cell Carcinoma in 40 Patients With Advanced Disease**

Site	No. patients (%)
Trunk	11 (28)
Upper extremity	11 (28)
Lower extremity	11 (28)
Inguinal lymph nodes <sup>a</sup>	4 (10)
Axillary lymph nodes <sup>a</sup>	1 (2)
Soft tissue metastasis <sup>a</sup>	1 (2)
Extensive pelvic metastases	1 (2)

<sup>a</sup>Primary tumor treated prior to presentation.

**TABLE III. Pathologic Stage of Squamous Cell Carcinoma in 40 Patients With Advanced Disease**

Factor	n	(%)
Stage <sup>a</sup>		
I	3	8
II	5	12
III	21	52
IV	11	28
Grade <sup>b</sup>		
Gx	1	2
G1	16	40
G2	12	30
G3	11	28

<sup>a</sup>Pathologic stage: American Joint Committee on Cancer (AJCC), 1993.

<sup>b</sup>Histopathologic grade, AJCC, 1993.

SCC arise in a burn scar and one patient (2%) had a history of active psoriasis for >30 years.

The sites of disease are listed in Table II. Metastatic disease was evident upon presentation in 17 patients (42%). This included eight patients with regional lymph node metastases, three patients with subcutaneous intranodal metastases, two patients with regional nodal and intranodal metastases, and one patient with nonregional nodal metastases. The remaining three patients had a combination of distant and nodal metastases. Pathologic analysis of suspicious regional nodes failed to confirm the presence of tumor in one patient. Thus the majority of patients presented with advanced stage disease (Table III).

The median follow-up from time of referral to RPCI was 24.0 months (range 3–144 months). At the time of last follow-up, 13 patients (32%) were alive with no evidence of disease. Sixteen patients (40%) had died of SCC, and 11 patients (28%) had died of other causes. The median survival was 28.0 months (range 0–144 months). The overall survival at 5 years was 43%.

Surgical therapy was performed in 38 of the 40 patients (95%). The remaining two patients received surgical therapy prior to transfer to our institution. This included one patient who was referred for photodynamic therapy for a local recurrence following a digital ampu-

tation and one patient who was treated with systemic chemotherapy for metastatic disease. Wide excision of the squamous cell carcinoma alone was performed in seven patients and was combined with a lymph node dissection in another eight patients. Amputation was required in nine patients. Lymph node dissection alone was performed in seven patients. Hemipelvectomy was performed in three patients and hemicorporectomy in one patient. One patient with extensive lower extremity disease refused amputation and underwent placement of an intra-arterial catheter for chemotherapy. This patient had no response to chemotherapy and ultimately required an above-the-knee amputation. Another patient underwent resection of a cervical subcutaneous metastasis and radical neck dissection, and one patient underwent open drainage of an abscessed pelvic tumor for palliation. Resection of the primary tumor commonly required a split thickness skin graft (four patients) or a flap (seven patients) for closure. Of the 15 patients who underwent lymph node dissection, the procedure was classified as therapeutic in 13 patients. Two patients with clinically nonpalpable lymph nodes underwent elective node dissection.

Paraneoplastic syndrome was noted in eight patients, which included seven patients with hypercalcemia and one patient with hyponatremia secondary to the syndrome of inappropriate antidiuretic hormone (SIADH). Following complete resection of a 12 cm subcutaneous metastasis, the patient with SIADH had normalization of the serum sodium level. This patient had an early recurrence of tumor 2 months following resection and expired 1 month later. Complete resection of the tumor was possible in two of these seven patients with hypercalcemia, following which the serum calcium returned to normal. However, both of these patients experienced early recurrence of tumor despite potentially curative resection and ultimately expired from their disease. In the remaining patients, residual tumor was present locally or in distant metastases and serum calcium levels remained elevated until the time of death from advanced disease. Median survival of the patients who presented with a paraneoplastic syndrome was 6.5 months.

Pathologic examination of resected specimens documented the status of the margins of resection in 32 of the 40 patients. Margins were classified as involved with tumor in three of 32 patients (9%). Surgical therapy was deemed palliative in two of these three patients. The remaining patient received adjuvant brachytherapy. The surgical margin was >1.0 mm from the tumor in five patients and ≤1.0 mm in two patients. The margin was classified as negative with no width specified in 22 patients. Therefore, 29 of the 32 patients (91%) had histologically negative margins. There were no 5-year survivors among the five patients with tumor at or within 1.0 mm from the surgical margin. Patients with negative

**TABLE IV. Univariate Analysis of Factors Affecting Survival in Patients With Advanced Squamous Cell Carcinoma of the Trunk and Extremity**

Factor	Median survival (mo)	5-yr survival (%)	P
Grade <sup>a</sup>			
well	48	46	0.94
moderately	18	33	
poor	60	55	
Age			0.9
Sex			
male	15	34	0.69
female	61	57	
Location			
extremity	61	51	0.09
trunk	7	18	
metastases	60	57	
Depth of invasion			
skin		100	0.06
subcutaneous	48	40	
soft tissue	28	36	
bone	7	18	
Stage <sup>a</sup>			
I		100	0.04
II		50	
III	25	48	
IV	10	18	
Type of surgery			
wide excision+/-LND <sup>c</sup>		57	0.009
LND alone	89	57	
amputation	28	28	
other	5	14	
Margins			
positive	0	0	0.005
negative ≤ 1mm	3	0	
negative not specified	18	40	
negative > 1mm	60	100	
Size of primary (cm)			
0-2		78	0.0001
>2-5	34	39	
>5-10	61	60	
>10	3	0	

<sup>a</sup>Grade information not available for one patient.

<sup>b</sup>American Joint Committee on cancer stage.

<sup>c</sup>Lymph node dissection.

margins with a distance not specified had a 5-year survival of 40%. Among the five patients with margins negative at >1.0 mm, 5 year survival was 100%. This difference was statistically significant ( $P = .005$ ).

Of the 36 patients surviving initial therapeutic attempts, 11 patients (31%) developed a recurrence. Recurrences consisted of local disease in seven patients (64%), intransit metastases in three patients (27%), and distant metastases in one patient (9%). Recurrences were treated by a variety of methods, which consisted of surgical therapy (six patients), external beam radiotherapy (three patients), and systemic chemotherapy (one patient). The median time to recurrence was 2.0 months with a range of 1-32 months. Median survival for the

**TABLE V. Multivariate Analysis of Factors Affecting Survival of Patients With Advanced Squamous Cell Carcinoma of the Trunk and Extremity**

Factor	<i>P</i>
Sex	0.75
Primary margins	0.30
Type of surgery	0.15
Age	0.08
Depth of invasion	0.08
Stage	0.04
Size of primary	0.02

**TABLE VI. Morbidity Following Resection of Advanced Cutaneous Squamous Cell Carcinoma of the Trunk and Extremity in 38 Patients Treated With Surgical Therapy**

Complication	No. patients (%)
Wound infection <sup>a</sup>	6 (16)
Flap necrosis	4 (10)
Pneumonia <sup>a</sup>	3 (8)
Ureteral injury	1 (3)
Bleeding	1 (3)
Lymphedema	1 (3)
Myocardial infarction	1 (3)

<sup>a</sup>One patient had both pneumonia and wound infection.

group of patients with recurrence was 13.0 months (range 3–81 months).

Lymph node dissection was performed in 15 patients and involved a radical groin dissection in nine patients, axillary dissection in five patients, and radical neck dissection in one patient. Node dissection was classified as therapeutic in 13 patients and elective in two patients. Both elective node dissections were performed in patients who had a history of intransit metastases from an extremity primary resected prior to referral to RPCI. Metastases were present in the resected lymph nodes in one of these patients. In addition to the 15 patients who underwent node dissection, five patients underwent a nodal dissection as part of a major amputation. Overall, four dissections were considered elective and 16 therapeutic.

Factors analyzed for effect on survival are listed in Table IV. By univariate analysis, tumor stage, the size of the primary tumor, the type of procedure, and margin status were found to be statistically significant. By multivariate analysis (Table V), only stage and smaller tumor size were found to have prognostic significance.

Thirty-day surgical mortality was observed in four patients (11%). Major surgical morbidity was encountered in 16 patients (42%) (Table VI). Neither the age, smoking history, location of the primary, size of the primary, presence of metastatic disease, or the performance of a lymph node dissection was associated with an increase in the incidence of postoperative complications. Only the stage of the tumor predicted development of a postoperative complication ( $P = 0.02$ ).

## DISCUSSION

Squamous cell carcinoma of the skin usually presents at an early stage amenable to cure by a wide variety of therapeutic modalities including radiation [5], cryosurgery [6], and surgical excision. In some cases, patients may present with advanced disease due to neglect or delayed recognition. An aggressive and radical surgical approach may be required to achieve control of the disease. Chronic sun exposure is related to the development of cutaneous cancers, explaining the predominance of extremity lesions [7]. In our series, 40% of the primary tumors were associated with an underlying chronic inflammatory condition, which may explain the high incidence of truncal tumors.

The incidence of metastases from SCC of the skin ranges from 0.1% to 20% in various series [7–9]. Metastatic disease was present in 42% of our patients. This high rate of metastases can be attributed to referral bias. In addition, the incidence of metastases had been found to be higher for patients with nonsun-induced squamous carcinomas [10–12]. This group forms a large part of the present series. Patient neglect and delayed recognition by the physician contribute to SCC presenting at an advanced stage. Nonhealing ulcers, changes in old scars, or draining sinus tracts must be suspected of SCC and should be subjected to biopsy.

Eight of our patients presented with a serum electrolyte abnormality, which in the absence of an identifiable etiology was presumed to be due to a paraneoplastic syndrome. Seven patients had hypercalcemia, which may have been secondary to ectopic production of a parathyroid hormone-type substance. An elevation of the serum PTH level was confirmed in one patient. This finding has been described in a case report by Marino et al. [13]. Normal keratinocytes produce parathyroid hormone-related proteins, and it is postulated that elevated levels of parathyroid related hormone produced by the epidermal cells are responsible [14]. In two patients with an elevated serum calcium, levels returned to normal with complete resection of the tumor, whereas those patients with residual disease had persistently elevated calcium levels. Both of the patients with complete resection of tumor and normalization of serum calcium experienced early recurrence. Overall survival for patients with a paraneoplastic syndrome was 6.5 months.

Overall 5-year survival for this series was 43%. Tumor stage was found to influence survival. The 5-year survival was 100%, 50%, 48%, and 18% for Stages I, II, III, and IV, respectively ( $P = 0.04$ ). The importance of stage was also noted by Shiu and others [15] who characterized patients with locally advanced disease without involved nodes as Stage I and patients with involved lymph nodes as Stage II. Five-year survivals of 71% and 57% for Stages I and II respectively were observed. Tumor size

also was noted to have prognostic significance both on univariate and multivariate analysis. In Shiu's series, the median survival for patients with tumors >10 cm was 3 months, and there were no 5-year survivors. We corroborate the importance of the size of the primary tumor and report no 5-year survivors in those patients with tumors >10 cm in size.

Shiu et al [15] reported that depth of invasion was important and noted no survivors among those patients with bony invasion. Depth of penetration was associated with worse survival and approached statistical significance in our series ( $P = 0.06$ ). The 5-year survival was 18% in those patients with bone invasion. Success in these patients may justify aggressive resection including amputation.

The margin of resection was found to be important by univariate analysis. Patients with margins >1 mm had a 100% 5-year survival compared with 40% for those with negative margins with the distance not specified and 0% for patients with tumor at or within 1 mm of the margin of resection ( $p = 0.005$ ). Although significant by univariate analysis, this factor was not identified as significant by multivariate analysis.

The role of lymph node dissection is not clear. If regional lymph nodes are involved clinically, biopsy is recommended, and if clinical suspicion is confirmed, a therapeutic dissection should be performed. The role of elective node dissection in patients with advanced cutaneous SCC remains to be defined. The small number of patients treated with an elective node dissection precludes a definitive statement its utility for SCC. Sentinel node biopsy techniques currently being investigated in the management of patients with melanoma may have a role in the care of patients with this disease as well.

Primary radiation therapy can be effective for cutaneous SCC. Hliniak et al. [16] reported a local control rate of 50% with primary external beam radiation. Shimm and Wilder [5] reported a 5-year, disease-free survival of 54% for patients treated with primary radiotherapy. Combined surgery and radiotherapy yielded a 5-year, disease-free survival of 79%, suggesting an improvement with combined therapy. Although this series contained patients with regionally advanced or recurrent tumors, only seven of the 85 patients had a primary skin tumor at a site other than the skin of the head and neck. In Shiu's series, radiotherapy was used as primary treatment in 10 patients and for recurrences in five patients [15]. Objective response was noted in nine of these 15 patients, and disappearance of tumor was noted in one patient. Radiation also was found to be effective in palliation of pain. However, there were no long-term survivors in this group, and death resulted from 3–11 months after treatment. In our series, radiotherapy was primarily used for palliation; however, the use of adjuvant radiotherapy is attractive as it allows widefield treatment beyond the

surgical bed to eradicate undetectable residual disease or intransit metastases. In addition, therapy to the regional nodes may be delivered, although the role for this therapy is not defined.

Chemotherapy has been utilized with success in patients with advanced SCC. Sadek et al. [17] reported a complete response (CR) of 30% and a partial response (PR) of 54% using a regimen of cisplatin, 5-fluorouracil (5-FU), and bleomycin. This induction regimen allowed long-term local control to be achieved in 50% of patients with definitive surgery or radiotherapy. This form of therapy may reduce tumor mass and allow for improved functional and cosmetic results from standard surgical therapy. Similar success was reported by Khansur and Kennedy [18] using systemic cis-platin and 5-FU. In this series of seven patients, CR was reported in three patients and PR in three patients for an overall response rate of 86%. Furthermore, one patient remained disease-free after 24 months of follow-up. Intralesional therapy with interferon alfa-2b also has been reported to have a complete response rate of 88% in patients with tumors ranging in size from 0.5 cm to 2.0 cm [19]. Other investigators have reported an overall response rate of 68% and a complete response rate of 25% using a combination of oral 13-*cis*-retinoic acid and subcutaneous interferon alfa-2a. Toxicity was mild and the median duration of response was 5 months [20]. This therapy may have promise in the neoadjuvant or adjuvant setting.

Extensive surgical resections are often required for control of advanced SCC. In 1962, Aust and Absolon [21] reported the first successful hemi-corporectomy that was performed for treatment of a SCC arising in a sacral decubitis. In our series, surgical procedures involved amputation in nine patients, hemipelvectomy in three patients, and hemi-corporectomy in one patient. Another indication of the extent of the surgical procedures required for control of disease is the low rate in which primary closure could be achieved. Flap closure was required in seven and split thickness skin grafting in four of the 38 patients undergoing surgical therapy. Unfortunately, the performance of aggressive surgical resections is not without cost. In our series, postoperative complications were frequent (42%) and mortality was 11%.

## CONCLUSIONS

In summary, a small subset of patients with cutaneous SCC of the trunk and extremity will present with advanced disease. Survival is stage dependent and the presence of a paraneoplastic syndrome is a poor prognostic factor. Treatment should consist of surgical resection with uninvolved margins of resection. In some cases this may require amputation. The role of elective lymph node dissection remains undefined. As extensive surgical resections are often required, investigation of treatment modalities useful in the neoadjuvant setting should con-

tinue with the goal of improving functional and cosmetic outcome.

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